Screening of immigrants in the UK for latent tuberculosis

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Tuberculosis (TB) is a serious public health problem in the UK, and detection and prophylactic treatment of latent infection offers improved control. A recent study advocates the use of IFN-γ release assays to detect latent TB infection in immigrants to the UK under 35 years of age and suggests that such a program would be most cost effective if targeted at new entrants from high burden countries. We discuss these findings in the light of recently updated UK and European guidelines. We conclude that while action to contain TB in the UK is urgently needed, further evidence is required to assess the impact and cost–effectiveness of screening algorithms for latent infection.

Keywords: cost–effectiveness • IFN-γ release assay • latent tuberculosis • screening • tuberculosis

Tuberculosis (TB) is a serious and emerging problem in the UK where over 9000 cases are recorded annually [101]. Data from the Health Protection Agency shows that over 70% of UK TB cases are born outside of the country leading to the supposition that treatment of latent Mycobacterium tuberculosis (Mtb) infection in immigrants would, by reducing the progression to active disease, decrease the prevalence of TB [101]. The recently published article by Pareek and colleagues investigates the cost–effectiveness of a strategy for screening immigrants for latent Mtb infection using an IFN-γ release assay (IGRA) [1]. There are two commercial IGRA currently available, the QuantiFERON®-TB Gold In-Tube assay (Cellestis Ltd., Victoria, Australia) and the T-SPOT®.TB (Oxford Immunotec, Oxfordshire, UK) [102]. They measure IFN-γ released following the incubation of patient blood with antigens specific to Mtb; early secretory antigenic target-6, culture filtrate protein 10, and the TB7.7 antigens. A positive test indicates an immune response to the Mtb antigens and it is not yet known how long an IGRA remains positive following infection, or following the successful treatment of active TB. IGRA are not specific to latent infection and it is necessary to exclude active TB disease prior to initiating prophylactic treatment to avoid the emergence of drug resistance through inappropriate therapy. In addition, a negative IGRA result does not exclude Mtb infection or active TB disease [2,3]. A further consideration is that treatment for latent infection incurs a risk of toxic side effects and UK guidelines recommend that individual risks and benefits be considered before treatment is offered to people over 35 years of age [103]. The UK NICE guidelines regarding latent TB and screening new entrants were revised in March 2011 [103]. We discuss the findings from the study by Pareek and colleagues in the light of the new NICE recommendations and comment on implications for TB control in the UK, highlighting areas that require further research.

Summary of methods & results
Pareek and colleagues undertook analysis of data collected in three referral centers in the UK that have implemented the QuantiFERON-TB Gold In-Tube for screening foreign born persons for latent Mtb infection. The centers studied were Westminster (London, UK), Leeds and Blackburn and all participants were aged 35 years or younger and within the first 5 years of their arrival in the UK. Symptomatic individuals and
those with a positive IGRA test were assessed for active TB by chest radiography and further clinical assessment. Of 1361 immigrants screened, five (0.04%) were found with active TB. Of 1229 individuals included in the final analysis, 245 (20%) were found positive with the IGRA test. Logistic regression found the factors associated with a positive IGRA test result were male sex (p = 0.046), increasing age (p < 0.0001) and TB incidence in the country of origin (p = 0.0006). Lack of data prevented Mycobacterium bovis bacillus Calmette–Güérin (BCG) vaccine status and HIV infection in the multivariate analysis. The authors present the yield of positive IGRA test results stratified by the prevalence of TB in the country of origin and by age. The new NICE guidelines recommend offering a test for latent infection being included to new arrivals under the age of 35 years from countries with a TB prevalence greater than 40 cases per 100,000 of the population [103]. A total of 99% of the immigrants tested fell into this category and no additional latent infections were detected in the 13 immigrants who originated in countries with low prevalence of TB.

Economic analysis was undertaken from the health provider perspective on a hypothetical cohort of 10,000 immigrants. The number of TB cases averted during 20 years following therapy for latent infection was estimated using data derived from a systematic review of the literature. A decision tree was constructed and sensitivity analysis undertaken. An estimated 95 active TB cases were predicted to occur if no treatment for latent infection was given, with an estimated associated cost to the health service of GB£600,000. Screening immigrants according to the 2011 NICE guidelines reduced the predicted number of active cases to 51, but at a cost of more than £1.5 million. Cost–effectiveness increased if screening was restricted to immigrants from countries with higher burdens of TB. With TB incidence thresholds of 250, 150 and 40 per 100,000, the incremental cost–effectiveness ratio per active case averted was £17,956, £208,819 and £29,403, respectively. The incremental cost–effectiveness ratio per case averted for screening all 16–35 year olds, regardless of country of origin, was £101,938.

**Expert commentary**

Guidance issued in 2011 by the European Centre for Disease Prevention and Control suggests that to identify individuals with latent Mtb infection for whom preventive treatment could be considered, IGRA should be used as part of an overall risk assessment [2]. NICE guidelines advocate their use when screening new entrants from high burden countries. A recent survey of primary care organizations in the UK demonstrated considerable heterogeneity in screening algorithms and in the proportion of immigrants found with latent TB infection, ranging from 4 to 33% [4]. Pareek and colleagues have shown that the cost–effectiveness of screening for latent infection may be enhanced by selective testing of immigrants at the highest risk and that the prevalence of TB in the country of origin is a key factor [1]. However, sensitivity analysis demonstrated that accurate estimates of some components in their decision model were crucial. A critical factor was the proportion progressing to active disease over the 20-year period. This outcome will be influenced by a number of factors that were not taken into account during the study, including the prevalence of confounding conditions such as coinfection with HIV. An additional consideration is the length of time those tested remained resident in the UK as it is likely that a proportion of immigrants with latent infection will leave the UK before progressing to active disease. Approximately a third of UK immigrants are students, of which two-thirds expect to stay in the country for less than 2 years and only 6% expect to stay more than 4 years [104]. In addition, the model did not take into account TB cases in immigrants arising from exposure subsequent to their arrival in the UK – for example, during visits to their home country. The specificity of the IGRA test was also important and further research is needed to compare the efficacy of screening algorithms in the UK [5].

In general, IGRA tests are commercial laboratory-based biological assays that require the transportation of blood samples to the laboratory under controlled conditions. It might be expected that additional costs would be incurred when compared with other methods of testing for latent infection, such as the tuberculin skin test. The lack of a test able to differentiate latent Mtb infection from active clinical disease is a hindrance to TB control. Of particular concern is the exclusion of extrapolmonary disease. Rates of resistance to isoniazid are elevated in extrapolmonary cases in the UK and inappropriate use of latent monotherapy would exacerbate this problem [101]. The majority of persons with a positive IGRA test will not progress to active disease and a test that predicts with greater accuracy the likelihood of developing TB would be of great benefit. Ideally such a test should be a point-of-care testing device that would avoid referral to a laboratory [6].

There were an estimated 590,000 immigrants to the UK during 2008, and excluding persons from the EU, the majority originate from countries in Asia and Africa with high burdens of TB [104]. The number arriving from four high burden countries is presented in **Table 1**. With an estimated 84% sensitivity screening by IGRA would leave a considerable pool of undetected latent infection in these populations. Approximately half the immigrants to the UK are older than 35 years of age. In their article, Pareek and colleagues do not consider a strategy to prevent TB in this population. A proportion of immigrants

<table>
<thead>
<tr>
<th>Country of last residence</th>
<th>Immigrants to the UK (1000s)</th>
<th>Estimated TB incidence per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>47</td>
<td>168</td>
</tr>
<tr>
<td>Pakistan</td>
<td>19</td>
<td>231</td>
</tr>
<tr>
<td>South Africa</td>
<td>20</td>
<td>960</td>
</tr>
<tr>
<td>China</td>
<td>18</td>
<td>97</td>
</tr>
</tbody>
</table>

may be screened though other programs. NICE guidelines currently recommend the screening of health service employees who have recently arrived from high-incidence countries and all persons at risk who are immunocompromised. Other inventions that may contribute to a reduction in the burden of TB in the UK include enhanced contact tracing and screening for other high-risk groups. It is also important that awareness is increased among health professionals and community organisations. Stigmatization of immigrant groups and individuals must be avoided.

**Five-year view**
The unacceptable level of TB in the UK demands action. Screening for recently arrived immigrants for latent disease would offer a partial solution. However, the impact on case notification ratios of screening a limited age range (under 35 years of age) remains unclear and will depend on factors that have not been examined in the article by Pareek and colleagues. The number of UK cases averted by screening new entrants will be assessed, where TB may result from infection or reinfection some time after arrival in the UK. Current testing strategies are restricted by the need to use sophisticated laboratory-based tests and the difficulties of differentiating latent infection from active disease. The development of improved tests is awaited but until the arrival of accurate point-of-care diagnostic tests and technology that can predict progression to active disease it is necessary to implement screening algorithms that are appropriate and effective. Screening for latent infection in new arrivals at risk of TB should be expanded, and research undertaken, in order to establish best practice. The proposed reorganisation of commissioning within NHS may alter referral patterns and coordination of TB control in the UK. It is important that the changes are tailored to assist and promote activities to reduce the incidence of TB.

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**Key issues**

- TB is a global health problem and high incidences are observed in many countries in Africa and Asia.
- In the UK, case-notification rates are increasing and London now has levels of disease exceeding 44 per 100,000 of the population.
- Over 70% of incident TB cases in the UK are in people born overseas and NICE guidelines issued in 2011 recommend screening for latent infection in new entrants under 35 years of age from countries with a TB prevalence greater than 40 per 100,000.
- The efficiency of screening is adversely affected by the lack of a test that can differentiate latent infection and active disease. This is particularly a concern with extrapulmonary forms of TB that are difficult to diagnose.
- Data analysis by Pareek and colleagues collected in UK referral centers that screen new entrants under 35 years of age for latent infection revealed that male sex, increasing age and increased incidence of TB in country of origin were associated with a positive test result.
- Incremental cost–effectiveness ratios per active case averted when using an IFN-γ release assay to screen for latent TB demonstrated that targeted screening of individuals from high burden countries improved the cost–effectiveness of the intervention.
- Further evidence is needed regarding the effectiveness and impact of screening strategies for latent infection in immigrants in the UK. Evidence is also needed regarding the contribution of other components of the strategy to control TB in the UK.
- There is uncertainty as to the future administration of TB control in the UK owing to the proposed restructuring of commissioning within the public health service.

**References**
Papers of special note have been highlighted as:
• of interest
•• of considerable interest


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